Acute stress disorder and C-reactive protein in patients with acute myocardial infarction

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Abstract: Background: Myocardial infarction-triggered acute stress disorder (ASD) and subclinical inflammation associate with the development of posttraumatic stress disorder, and worsen the prognosis of myocardial infarction patients. We examined the relationship between ASD severity and C-reactive protein levels in patients with acute myocardial infarction. Method: We assessed 190 patients (median age 59 years; 83% men) with a verified myocardial infarction within 48 h of an acute coronary intervention. Circulating levels of C-reactive protein were categorized according to their prognostic risk for cardiovascular disease: 0 to <5, 5 to <10, 10 to <20, and 20 mg/l. Patients completed the ASD-Scale (ASDS) for myocardial infarction-triggered symptoms and questionnaires for demographic factors, health behaviours, cardiac-related variables and psychosocial characteristics. Results: The ASDS sum score was positively associated with C-reactive protein categories in the bivariate analysis ($r = 0.20$, $p < 0.01$). Significant relationships with C-reactive protein also emerged for dissociation ($r = 0.25$, $p < 0.001$) and avoidance ($r = 0.19$, $p < 0.01$), but not for arousal and re-experiencing. Similarly, C-reactive protein levels 20 mg/l versus < 20 mg/l were predicted by the ASDS sum score, and the dissociation, avoidance and arousal subscores (all p-values < 0.05) in the fully adjusted binary regression analyses. C-reactive protein levels 20 mg/l were also independently predicted by male gender, body mass index, lower education, and lower left ventricular ejection fraction and higher white blood cell count. Conclusions: Higher levels of myocardial infarction-triggered ASD symptoms associate with a greater inflammatory response in patients with acute myocardial infarction independently of important covariates. The findings suggest a link between myocardial infarction-triggered ASD symptoms and a heightened acute phase response with a potential impact on cardiovascular disease prognosis.

DOI: https://doi.org/10.1177/2047487317748506

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Short title: Acute stress disorder and CRP in acute MI

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ABSTRACT

Background: Myocardial infarction (MI)-triggered acute stress disorder (ASD) and subclinical inflammation associate with the development of posttraumatic stress disorder, and worsen the prognosis of MI patients. We examined the relationship between ASD severity and C-reactive protein (CRP) levels in patients with acute MI.

Methods: We assessed 190 patients (median age 59 years; 83% men) with a verified MI within 48 h of an acute coronary intervention. Circulating levels of CRP were categorized according to their prognostic risk for cardiovascular disease (CVD): 0 to <5, 5 to <10, 10 to <20, and ≥20mg/L. Patients completed the ASD-Scale (ASDS) for MI triggered symptoms and questionnaires for demographic factors, health behaviors, cardiac-related variables, and psychosocial characteristics.

Results: The ASDS sum score was positively associated with CRP categories in the bivariate analysis ($r=0.20$, $p<0.01$). Significant relationships with CRP also emerged for dissociation ($r=0.25$, $p<0.001$) and avoidance ($r=0.19$, $p<0.01$), but not for arousal and re-experiencing. Similarly, CRP levels ≥20mg/L versus <20mg/L were predicted by the ASDS

sum score, and the dissociation, avoidance and arousal subscores (all p-values <0.05) in the fully adjusted binary regression analyses. CRP levels ≥20mg/L were also independently predicted by male gender, BMI, lower education, and lower left ventricular ejection fraction, and higher white blood cell count.

Conclusions: Higher levels of MI-triggered ASD symptoms associate with a greater inflammatory response in patients with acute MI independently of important covariates. The findings suggest a link between MI-triggered ASD symptoms and a heightened acute phase response with a potential impact on CVD prognosis.

Keywords: Cardiovascular disease; inflammation; psychobiology; risk factor; trauma stress

INTRODUCTION

Acute stress disorder (ASD) is a mental disorder that develops within 4 weeks of a traumatic event and, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, is characterized by symptoms of dissociation, re-experiencing, avoidance and hyperarousal. In patients with acute coronary syndrome (ACS), such as myocardial infarction (MI), the prevalence of ASD was found to be 18% when assessed with a clinical questionnaire (1). ASD is regarded as a risk factor for the development of posttraumatic stress disorder (PTSD) (2) that associates with impaired quality of life (3) and adverse cardiovascular outcome after ACS (4,5).

Low grade inflammation is now considered a major risk factor for cardiovascular diseases (CVD) (6), and it is also involved in the pathophysiology of PTSD (7), specifically found for the elevation in the inflammatory marker C-reactive protein (CRP) (8). As such, elevated levels of high sensitive (hs)CRP predicted the prognosis for incident CVD events

and mortality, with a pronounced effect for high concentrations (>10 mg/L) (9), and also for 1-year mortality (10,11).

Fear of dying showed in ACS patients a positive association with the inflammatory biomarker tumor necrosis factor-α upon hospital admission (12). However, it has not previously been investigated whether ASD directly relates to CRP risk categories during ACS. We therefore examined the relationship between ASD symptom severity and CRP levels in patients with high peritraumatic distress due to acute MI, differentiating for dissociation, re-experiencing, avoidance and arousal symptoms, which differently predicted resilience (13) and long-term prognosis in previous ACS studies (14,15). We controlled for relevant sociodemographics, health behaviors, cardiac-related variables and psychosocial characteristics.

MATERIALS AND METHODS

Patients and study design

Between January 2013 and September 2015, the Myocardial Infarction-Stress Prevention Intervention (MI-SPRINT) study recruited a sample of 190 eligible patients from the Bern University Hospital ("Inselspital") referred for acute coronary care intervention due to verified acute ST-elevation MI (STEMI) or non-STEMI. MI-SPRINT is a randomized controlled trial evaluating the effects of early psychological counseling on the development of posttraumatic stress at 3 months follow-up (16). Patients were informed and gave signed consent to the study which was approved by the ethics committee of the State of Bern, Switzerland (KEK-Nr. 170/12). The study complies with the Declaration of Helsinki. Included were participants 18 years or older with a need for counseling due to a substantial level of acute distress perceived during MI (score of at least 5 for chest pain and for fear of dying and/or helplessness on a numeric rating scale from 0-10) (17). All patients underwent a

structured clinical interview within 48 h after having reached stable hemodynamic conditions. Medical history data, lifestyle/health behaviors, self-rated and validated psychometric questionnaire data were collected combined with a fasting venous blood sample for the assessment of CRP the next morning (note that for logistical reasons, blood was collected at another time of the day in 17 cases and non-fasting in 12 cases). Exclusion criteria were emergency coronary artery bypass grafting, any serious comorbid disease likely to cause death within one year, cognitive disorientation and impairment, current severe depression (per the cardiologists' clinical judgement), suicidal ideations in the last two weeks, insufficient knowledge of German language, and participation in another randomized controlled trial in the cardiology department.

Measures

We used the German version of the ASD-Scale (ASDS) to assess the prevalence of psychiatric symptoms of acute distress induced by MI (18). According to the DSM-IV (Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994), it provides an index value from a 19-item self-report inventory according to DSM-IV ASD criteria (19). The ASDS comprises four subscales referring to ASD symptoms of dissociation (5 items), re-experiencing (4 items), avoidance (4 items) and arousal (6 items). Each item is scored on a 5-point Likert scale from 0 ("not at all") to 4 ("extremely"). Sum scores range between 0 and 76, with higher values indicating more stress. All participants were asked to rate the questionnaire with respect to the cardiac event. An ASDS sum score of 9 or greater for the dissociative symptom cluster in combination with a cumulative score of 28 or greater for the remaining 3 symptom clusters indicates a DSM-IV diagnosis of ASD with sensitivity of .95 and specificity of .83 (19).

Participants with coronary heart disease (CHD) rated pain intensity during MI with a numeric rating scale between 0 ("no pain at all") and 10 ("unbearable pain"). Perceived social support was assessed with the Enhancing Recovery in CHD Patients Social Support Inventory, comprising dimensions of emotional, structural and instrumental support, with six items on a Likert scale from 0 ("none of the time") to 4 ("all the time") (Mitchell et al. 2003). Socioeconomic status was defined with reference to a high, medium or low level of education (21). Participants further disclosed their weight and height for the calculation of the body mass index (BMI), smoking habits (current, former or never smokers), frequency of physical activity ("that makes you sweat") in an average week, and consumption of alcoholic beverages. According to the well-known J-shaped risk between alcohol intake and CVD risk (22), we categorized participants on a scale from 0-2 as moderate drinkers, non-drinkers, and heavy drinkers (>21 drinks/week for men, >14 drinks/week for women).

CVD-related measures were STEMI vs. non-STEMI (23) and the Global Registry of Acute Coronary Events (GRACE) risk score, which combines eight variables to estimate the risk of post-discharge death and recurrent MI after ACS (24). As markers of acute disease severity, we additionally included left ventricular ejection fraction (LVEF), obtained from angiography records, peak troponin T levels and white blood cell (WBC) count in the analyses. The acute-phase protein CRP was measured in lithium-heparin plasma with an Immunoturbidimetric assay (C-Reactive Protein Gen.3, measuring range 0.3-350 mg/L) using the COBAS 8000 c702 module from Roche Diagnostics. The assay was performed according to the manufacturer's instructions at the Central Laboratory for Clinical chemistry - CoreLab, Bern University Hospital, Switzerland. Circulating levels of CRP were categorized according to the prognostic risk of (hs)CRP levels for incident CVD: 0 to <5, 5 to <10, 10 to <20, and ≥20mg/L (9).

Statistical analyses

Data were analyzed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL) with level of significance at $p<0.05$ (two-sided). Information on ASDS and its subscales was missing in 40 cases each; CRP was not measured in 17 cases (8.9%).

The GRACE risk score could not be computed for 18 patients; 43 cases missed information on social support. Four or less values were missing for the other measures.

We replaced all missing values with the expectation maximization algorithm to make use of all the available information from the total sample of 190 study participants. Little's missing completely at random (MCAR) tests revealed no significant patterns before performing imputations. Student's t-test, Mann-Whitney U-test and Pearson Chi-square test, where appropriate, were used to calculate group differences between variables of interest. Spearman Rho's correlation analysis was used to estimate the bivariate relationship between two variables. To examine an independent effect of ASD symptoms on an excessive inflammatory stress response, we tested whether ASDS sum scores and subscores were significantly linked with CRP levels equal to or above 20 mg/L versus below 20mg/L, taking sociodemographics, health behaviors, cardiac-related variables and psychosocial factors into account (all variables entered in one block). We selected these covariates a priori based on the literature, as they might potentially confound associations with outcomes, as well as the type of psychological counseling as a control variable (trauma-focused vs. stress counseling) to adjust for a potential intervention effect. We allowed a maximum of 15 covariates to protect against model overfitting. Inspection of variance inflation factors indicated no concern for multicollinearity.

RESULTS

Patient characteristics

The characteristics of the 190 study participants as a whole and per CRP levels below vs. above the median value of 19.7 mg/L are shown in Table 1. The median age of the patient sample was 60 years (range 18-88). All were of Caucasian ethnicity, predominantly male and with a medium or high level of education. According to the GRACE score, the median risk of postdischarge death in the next six months was 5% (range 3-9). By study design, the average level of perceived acute pain during MI was substantial with a mean score of 7.92 (SD 1.66). The ASDS sum score ranged from 0 to 45 and reached the cutoff score of 28, fulfilling ASD diagnostic criteria, in 19 cases (i.e., 10% of the study sample).

Table 1 shows that participants with CRP levels above vs. below the median were more likely to be female and to have higher BMI, STEMI, and greater disease severity as per a higher WBC count, peak troponin level and GRACE score on the one hand and reduced LVEF on the other. Except for a more frequent application of prasugrel in patients above the median CRP level, medication frequency was similar in both groups.

Relationship of acute stress disorder symptoms with patient characteristics

ASDS scores were not normally distributed among participants. The mean (SD) ASDS sum score was 16.3 (8.8) and the median was 16 (range 0-45). Before imputation of missing values, CRP categories referring to CVD-risk were <5 mg/L in 34 (17.9%) patients, 5 to <10 mg/L in 20 (10.5%) patients, 10 to <20 mg/L in 32 (16.8%) patients and ≥20mg/L in 87 (45.8%) patients. In the 141 patients with complete data for these measures, the strength and significance of the relations between CRP categories and ASD sum score ($r=0.20$, $p<0.05$), dissociation ($r=0.24$, $p<0.01$) and avoidance ($r=0.18$, $p<0.05$), but not arousal ($r=0.14$, $p=0.09$) and re-experiencing ($r=-0.04$, $p=0.63$). These associations were similar to those for the whole sample with replaced missing data points. As shown in Table 2, the ASDS sum score correlated with the four categories of CRP levels ($r=0.20$, $p=0.006$). Of the

ASD subscales, the dissociation ($r=0.25$, $p<0.001$) and avoidance ($r=0.19$, $p<0.05$) scores were also positively correlated with CRP categories, while the re-experiencing and arousal scores showed no significant associations.

With regards to covariates, similar associations with ASDS scores as for CRP emerged for WBC count. Moreover, dissociation scores were higher in men than in women and in participants with less physical activity. Avoidance and arousal scores were both found increased in patients with lower levels of social support, while re-experiencing was higher in patients with a higher peak troponin level at admission. Besides, our data revealed no other significant correlation with any further demographic variables (age, education), health behavior (BMI, smoking, alcohol consumption) and cardiac-related variables (STEMI/non-STEMI, GRACE risk score). The intensity of acute pain during MI and the type of the psychological counseling intervention were also not significantly associated with ASD symptomatology.

Prediction analyses of an excessive inflammatory response in acute MI

Table 3 displays the results of the binary regression analyses, separately for the ASDS sum score and its sub-scores. In fully adjusted models, all ASDS scores, except the re-experiencing sub-score, emerged as consistent and independent predictors of CRP levels ≥20mg/L. Male gender, higher BMI, and white blood cell count were consistently associated with CRP levels ≥20mg/L, with a similar tendency for lower level of education and LVEF.

DISCUSSION

The present study is the first to examine the association between ASD symptom severity and the inflammatory response in patients with acute MI, taking into account potentially modulating effects of demographics, CVD risk factors, cardiac-related variables, and

psychosocial factors. We found a significant and direct correlation between ASDS and CRP across four categories of concentration levels. A total of 10% of our patients met the cut-off for an ASD case definition, a prevalence that is somewhat lower than previously reported (1). Therefore, the observed relation between ASDS and CRP levels may be relevant even at subthreshold levels of ASD (19). Following up on a current debate (14), ASDS scores below the cutoff of a DSM-IV ASD diagnosis ought to be considered as clinically relevant. This reasoning is substantiated by the observation that ASDS predicted CRP levels in the highest risk category ≥20mg/L in which almost half of our patients were represented. Importantly, this high risk for recurrent CVD events and mortality was independently predicted in addition by ASD severity, with the prognostic LVEF score, BMI, male gender, and low education.

These associations of ASD symptoms with very high CRP levels were particularly driven by symptoms of dissociation, avoidance and arousal, but not re-experiencing, in the fully adjusted analysis. Interestingly, we found social support to be a protective factor mitigating the development of arousal and avoidance symptoms in MI patients. This is in agreement with the paradigm of social support as a stress buffering variable (25), and studies showing low social support is a psychosocial risk factor of CVD (26,27). Accordingly, social isolation has been associated with increased CRP levels in a population-based study and both social isolation and CRP were predictive of death from CHD 15 years later (28). However, in our study, social support did not independently predict CRP levels above 20mg/L adjusted for other covariates as CRP reflected the acute phase response after a cardiac event more than a steady state chronic low-grade inflammation.

Previously, longitudinal data identified MI-triggered dissociative symptoms as a predictor of early mortality during 15-years of follow-up (15). In line with this finding, we found CRP risk categories to correlate strongest with the dissociation subscore (r=0.25) of all ASDS sub-sores. Moreover, males emerged to be at risk with regard to CRP levels equal or above

20mg/L as shown for ASD symptomatology in general and dissociation, which is in line with community based epidemiologic data on symptoms of dissociation in PTSD (29). Such vulnerability is surprising considering that women are more prone to develop PTSD after MI (30), and show also more frequently symptoms of anxiety and depression than men more than one year after hospitalisation due to CHD events (31). However, the low proportion of women in our sample precluded gender-stratified analyses.

As could be expected from the literature (32), our results support the relevance of a high BMI for CRP levels of 20mg/L or higher, independently of covariates. Similarly, we found that reduced LVEF and higher WBC count related to excessive CRP levels, whereas peak troponin levels and the prognostic GRACE score did not.. In view of the magnitude of these effects, we interpret that the independent relationship between MI-triggered ASD and CRP may be of clinical relevance. This may indicate a need for longitudinal studies to investigate if an excessive inflammatory response accounts for some of the poor clinical outcome in terms of an increased risk of recurrent CVD events and PTSD development.

Owing to the study design, our findings should not be generalized to the ACS population at large, as we included highly distressed patients with rather low additional psychiatric and somatic disease burden. A structured clinical interview would have yielded more reliable ASD symptoms than the self-rated questionnaire used in our study. The selection of covariates can be challenged (i.e. exclusion of history of depression), however in order to avoid overfitting of the model, we included a selection of potentially relevant predictors in the model based on theoretical assumptions. Although the applied assay detects CRP values as low as 0.3mg/L, we did not measure (hs)CRP that is traditionally used to predict CVD risk.

In summary, ASD placed individuals at heightened risk for inflammation in the setting of ACS as a life-threatening trauma. ASD severity predicted the presence of CRP

levels at 20mg/L or higher. This being a relevant threshold, our results could have important clinical implications. If symptoms of ASD set off peripheral inflammation, their early assessment as severe in ACS patients may indicate the need for immediate interventions such as fostering resilience (13). Future research is needed to test the hypothesis that the direction of causality runs from ASD via an inflammatory response to PTSD development in the aftermath of MI.

ACKNOWLEDGMENTS

This study was financially supported by grant No. 140960 from the Swiss National Science Foundation to RvK (PI), JPS, US, HZ and JB. Conflict of Interest: none declared.

AUTHORS CONTRIBUTIONS

All authors contributed to the conception or design of the work and interpretation of the data. HB and RvK performed data analysis. REML and MP contributed to the acquisition of the data. HB drafted the manuscript, which was critically revised by all co-authors. All authors gave final approval for submission of the manuscript and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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